Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 4000 Princeton, NJ 08543-4000

Worldwide Regulatory Affairs

September 2, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 99D- 154 1 - Draft Guidance for Industry on Establishing Pregnancy Registries

Dear Sir/Madam:

Reference is made to FDA's issuance of draft guidance for industry on establishing pregnancy registries (*Federal Register* 64:30041, June 4, 1999). This notice requested that written comments be submitted to FDA by September 2, 1999. The purpose of this letter is to provide comments on this draft guidance document.

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion. For these reasons, we are very interested in and well qualified to comment on this proposed Guidance.

Bristol-Myers Squibb is supportive of the FDA initiative to standardize the collection of pregnancy outcome information. However, we recommend that the development of any pregnancy registry be determined by potential risk to a mother or fetus and be based on clearly presented scientific evidence.

Purpose of Pregnancy Registries

While not directly stated in the Guidance, it appears implicit in the document that the purpose of a pregnancy registry is to provide scientifically-based outcome data in a timely manner to medical care providers for their patients who may need to use a particular medication during pregnancy or who have experienced an inadvertent drug exposure during pregnancy. As described in the Guidance, and consistent with current practice, significant adverse human pregnancy outcome information from a registry would be incorporated into the product label with appropriate warnings and precautions.

C4

99D-1541

However, it is unclear from the Guidance how normal pregnancy outcome findings from a registry will be used. Data on normal pregnancy outcomes following drug exposure are equally important to medical care providers and their patients. We suggest that the information collected by pregnancy registries on normal as well as abnormal outcomes be either incorporated into product labeling or disseminated through a national information system, such as the Organization of Teratogen Information Services (OTIS). Such a system could provide available pregnancy outcome information for a specific drug or drug class and, when appropriate, provide individualized risk assessment based on the type of exposure.

Focus and Criteria for Establishing Pregnancy Registries

We recommend that FDA clearly define the public health need for specific pregnancy registries/studies based on the likelihood of a drug's use during pregnancy and the potential risks of that compound to the mother or fetus. The establishment of a registry should be driven by a risk of adverse effects in human pregnancy based on a drug's chemical structure or principal metabolites, pharmacologic activity, similar mechanisms of action within a pharmaceutical class, animal reproductive toxicology studies, or human case reports.

We recommend that FDA consider national registries studies when there is concern for more than one drug in a class or when more than one therapeutic option for a given disease or medical condition pose a potential risk (e.g., anticonvulsant therapy). With the small number of pregnancy exposures for any drug, uniform data collection for all drugs of concern will provide the most useful information on potential exposure risks. In addition, national registries can assist in the data collection of the natural course of maternal disease during pregnancy including untreated disease and conditions treated with older, conventional therapy.

We encourage FDA to enlist patient advocacy groups (e.g., American Diabetes Association) and medical societies (e.g. American Rheumatology Society) to endorse or assist in the conduct of pregnancy registry studies. This will facilitate patient recruitment and maintain a focus on disease outcomes in pregnancy. We also encourage FDA to convene an expert panel which includes industry to prepare clear and specific public health goals for pregnancy registries and methods for establishing these registries.

The public health merit of a registry must be based on the scientific evidence for a potential risk and should demonstrate a cost benefit. Routinely establishing registries for drugs with an "unknown" risk in pregnancy would not be productive since this would include compounds with clean animal reproductive toxicology profiles and no reported human adverse pregnancy outcomes. In addition, registries are not needed for older, marketed drugs without reported adverse human pregnancy outcomes.

Design of Pregnancy Registries

Specific registry study designs should be determined in collaboration with the drug sponsor. In addition, clear endpoints for individual registries must be established before initiation so that registries can be brought to closure at a pre-determined point.

As outlined in the Guidance, a study design using matched controls may help to identify the potential risks associated with drug use during pregnancy sooner than other surveillance systems, but this method may be most useful as a sentinel identification system. Follow-up studies using more traditional epidemiologic methods may be required when specific adverse human

pregnancy outcomes are identified or suspected, particularly when evaluating events such as developmental delay, neurologic abnormalities, or other medical conditions which are diagnosed years after exposure.

Financial Support of the Registries
While the specifics of financial responsibilities for these programs were not addressed in the draft guidance, it seems obvious that the cost of such an undertaking will be significant. The issue needs to be addressed by FDA.

Promotion of Registries, Recruitment and Protocol Information
Because of promotional, recruitment and protocol information issues which may be raised by DDMAC, we request that these issues be resolved within FDA prior to the initiation of any registries and that clear guidance be available to sponsors.

Data Collection Tool (Attachment 1)
We agree with the importance of collecting a detailed medical history and maternal and neonatal clinical course and suggest that the following additional items be included:

- maternal disease course and complications during pregnancy
- additional non-drug exposures including maternal infections, x-rays, medical/surgical procedures, etc.

Bristol-Myers Squibb appreciates the opportunity to comment on this Guidance and we would be pleased to work with FDA in addressing the very important issues presented in the Guidance.

Sincerely,

Laurie Smaldone /jmKenney
Laurie Smaldone, M.D.
Senior Vice President
Worldwide Regulatory Affairs

Sol I. Rajfer /jmKenney
Sol I. Rajfer, M.D.
Senior Vice President
Worldwide Clinical Research & Development